

# Ocular penetration of topical ciprofloxacin and norfloxacin drops and their effect upon eyelid flora

John P Leeming, Jeremy P Diamond, Romane Trigg, Les White, H Bing Hoh, David L Easty

## Abstract

A double blind, prospective study was undertaken to compare aqueous humour penetration of topical 0.3% norfloxacin and 0.3% ciprofloxacin and their effect upon normal eyelid flora in 39 patients undergoing cataract surgery. Lid swabs were taken before and after six 1 hourly applications of single drops of ciprofloxacin or norfloxacin given before surgery. Aqueous humour was aspirated at surgery and antibiotic concentration assayed using high performance liquid chromatography. The mean aqueous humour concentrations were: ciprofloxacin 220 ng ml<sup>-1</sup>, norfloxacin 140 ng ml<sup>-1</sup>. Although this difference was not statistically significant ( $p=0.112$ ) the trend demonstrated may be relevant clinically, especially considering the greater activity of ciprofloxacin. Both coagulase negative staphylococcal ( $p=0.004$ ) and total bacterial ( $p=0.019$ ) lid counts dropped sixfold after ciprofloxacin treatment but the smaller reductions noted after norfloxacin application did not achieve statistical significance ( $p>0.1$ ). The reduction of external eye flora experienced with ciprofloxacin suggests that this may be a useful presurgical prophylactic agent.

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The fluoroquinolones are broad spectrum antibacterial agents with activity against many of the important ocular pathogens including staphylococci, *Neisseria gonorrhoea*, *Haemophilus influenza*, Enterobacteriaceae, and *Pseudomonas aeruginosa*.<sup>1–3</sup> Ophthalmic preparations of three fluoroquinolones (norfloxacin, ofloxacin, and ciprofloxacin) have been formulated, all in 0.3% solution. In addition to their potential as therapeutic agents in external eye infection<sup>4,5</sup> and keratitis,<sup>7,8</sup> they may be a good choice for prophylaxis against post-surgical endophthalmitis.

Antibiotic surgical prophylaxis has been advocated on the premise that it prevents postoperative endophthalmitis, both by reducing risk of autologous infection arising from adnexal bacterial flora and by killing organisms which contaminate the wound during surgery.<sup>9</sup> Thus, selection of a prophylactic antibiotic is dependent upon ability to reduce periorbital bacterial counts and to penetrate the surgical site in a concentration effective against likely pathogens.

While the fluoroquinolone antibiotics have similar spectra of activity they are not equally potent against many organisms and vary in their ability to penetrate closed organs.<sup>10</sup> Thus, the choice of fluoroquinolone to use either in prophylaxis against surgical infection or in treatment of established endophthalmitis is not clear.

This study was designed to investigate the

relative effectiveness of preoperative application of topical 0.3% ciprofloxacin and 0.3% norfloxacin, both in reducing eyelid flora and in penetrating the aqueous humour. The sensitivity of external ocular bacteria to the aqueous humour concentrations of each drug was also assessed.

## Materials and methods

Patients undergoing routine extracapsular cataract extraction under local or general anaesthetic and who had uninflamed eyes and normal corneal epithelium were studied. Exclusion criteria included topical antibiotic treatment during the previous 7 days, renal disease, or a history of allergy to quinolones. Informed consent was obtained from all subjects.

Patients were admitted to hospital early on the day of surgery and given six 1 hourly single drop doses of 0.3% ophthalmic preparations of either ciprofloxacin (Alcon) or norfloxacin (MSD) to the surgical eye. The antibiotic preparations were contained in unlabelled, coded bottles and randomly assigned such that the patient, clinician, microbiologist, and assay scientist were unaware of the identity of the drug prescribed. Patients received concurrent surgical preparation with unpreserved mydriatic drops. Where surgery was performed under local anaesthesia, topical anaesthetic drops were applied after the last antibiotic drop. Surgery was commenced between 10 and 60 minutes after instillation of the last drop, at which time 100–150 µl of aqueous humour were aspirated before opening the surgical section. Aqueous humour was snap frozen in liquid nitrogen and stored at –70°C until fluoroquinolone assay was undertaken.

Microbiological samples were taken on admission and immediately before surgery. An alginate swab was moistened in sterile Ringer's solution and rolled around the lid margin of the operative eye. The swab was dropped into 0.2 ml Ringer's solution and immediately delivered to the microbiology laboratory. On arrival, 1.8 ml Ringer's solution containing 10 g l<sup>-1</sup> sodium hexametaphosphate was added and the swab was vortex mixed for 1 minute to disperse alginate fibres (modified from Cagle and Abshire<sup>11</sup>). Bacteria were enumerated by standard methods on the surface of diagnostic sensitivity test agar (DST) plates (Unipath Ltd, Basingstoke, UK). The sensitivity of the method used was 4 colony forming units (CFU) per swab. To assess the proportion of external eye flora sensitive to the concentrations of fluoroquinolone in the eye, colony counts were also made on DST plates containing 0.2 mg l<sup>-1</sup> ciprofloxacin or norfloxacin for the last 13 patients studied. This concentration was chosen to reflect the concentrations of fluoroquinolone found in the aqueous humour in

University of Bristol,  
Department of  
Ophthalmology, Bristol  
Eye Hospital, Lower  
Maudlin Street, Bristol  
J P Diamond  
H B Hoh  
D L Easty

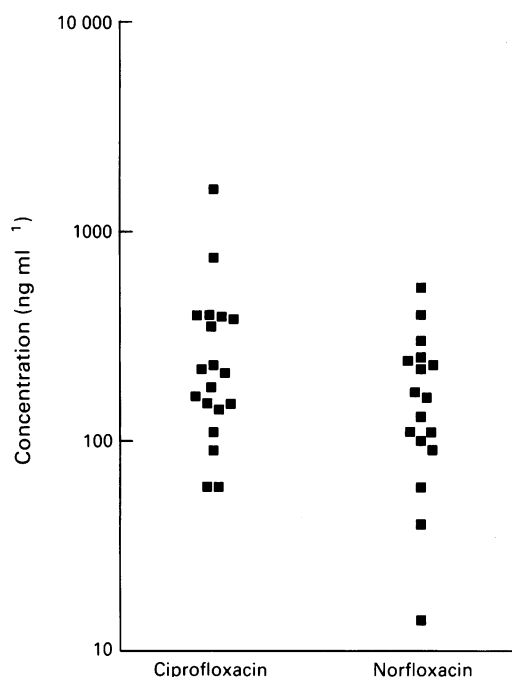
Bristol Public Health  
Laboratory, Bristol  
Royal Infirmary, Bristol  
J P Leeming  
R Trigg

Department of  
Microbiology,  
Southmead Hospital,  
Bristol  
L White

Correspondence to:  
Jeremy P Diamond,  
University of Bristol,  
Department of  
Ophthalmology, Bristol Eye  
Hospital, Bristol BS2 2LX.

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Figure 1 Quinolone concentrations in the aqueous humour of patients who received six hourly single drop doses of 0.3% ciprofloxacin or 0.3% norfloxacin eyedrops.



the early stages of the investigation. Colonies were counted after 2 days of aerobic incubation at 37°C.

The fluoroquinolone concentration in aqueous humour samples was assayed by high performance liquid chromatography (HPLC) using slight modifications of the method of Gau *et al*<sup>12-14</sup>

Aqueous humour quinolone concentrations and pre- and post-treatment bacterial counts were logarithmically transformed and compared statistically using paired *t* tests. The null hypothesis was rejected when  $p \leq 0.05$ .

### Results

A total of 39 patients were studied. Twenty six (66.7%) were females and 13 (33.3%) males. Mean age was 75.2 years (range 46–94 years).

The antibiotic concentrations found in aqueous humour are illustrated in Figure 1. The geometric mean values were: ciprofloxacin 220 ng ml<sup>-1</sup> ( $n=19$ , 95% confidence limits 150–330 ng ml<sup>-1</sup>), norfloxacin 140 ng ml<sup>-1</sup> ( $n=17$ , 95% confidence limits 90–220 ng ml<sup>-1</sup>). These differences were not statistically significant ( $p=0.112$ ). The aqueous humour samples from two patients were of insufficient volume for HPLC assay and a third sample was lost.

The mean bacterial counts from the pre- and post-treatment lid swabs are compared in Table 1. The coagulase negative staphylococci are presented separately as they represent the most common cause of postoperative endophthal-

mitis.<sup>15</sup> Swabs from two patients were unavailable for analysis.

A total of 13 pretreatment lid swabs were cultured onto DST agar containing 200 ng ml<sup>-1</sup> ciprofloxacin and norfloxacin. Although this concentration of ciprofloxacin suppressed colony counts markedly after 24 hours' incubation, after 48 hours counts did not differ significantly from those obtained on plain DST control plates (geometric mean staphylococcal counts per swab were DST=28.7, DST+ciprofloxacin=15.5 and DST+norfloxacin=25.5).

### Discussion

Several previous studies of penetration into rabbit and human aqueous humour of topical norfloxacin have been reported. Huber-Spitzky<sup>16</sup> gave topical 0.3% norfloxacin to patients undergoing cataract extraction and demonstrated mean aqueous humour concentrations of 660 ng ml<sup>-1</sup>. In similar investigations Behrens-Baumann<sup>17</sup> demonstrated mean aqueous humour norfloxacin concentrations of 14–105 ng ml<sup>-1</sup> and Bron and colleagues<sup>18</sup> found concentrations of 52–131 ng ml<sup>-1</sup>, depending upon frequency of administration. These investigators also applied single drops of 0.3% norfloxacin to rabbit eyes and demonstrated aqueous humour concentrations of 0.2 µg g<sup>-1</sup> (approximately 200 ng ml<sup>-1</sup>). If the antibiotic was given after removal of the corneal epithelium the corresponding concentration was 8.6 µg g<sup>-1</sup> (approximately 8600 ng ml<sup>-1</sup>).

There have been fewer reports concerning the penetration of ciprofloxacin. O'Brien *et al* detected mean aqueous humour ciprofloxacin concentrations of 4820 ng ml<sup>-1</sup> in rabbits with intact epithelia and 12 900 ng ml<sup>-1</sup> in rabbits with debrided corneal epithelia 30 minutes after application of three drops of 0.3% ciprofloxacin solution.<sup>19</sup> Reidy *et al* determined the penetration of 1% norfloxacin and 0.75% ciprofloxacin (11 drops) across rabbit corneas artificially infected with *Pseudomonas aeruginosa* to be 7500 ng ml<sup>-1</sup> and 305 500 ng ml<sup>-1</sup> respectively.<sup>20</sup> A preliminary communication of a comparative study of aqueous humour penetration of topical fluoroquinolones in humans reports mean concentrations of norfloxacin 46 ng ml<sup>-1</sup>, ciprofloxacin 72 ng ml<sup>-1</sup> and ofloxacin, which we did not study, 625 ng ml<sup>-1</sup>.<sup>21</sup> The observation that ofloxacin penetrates the cornea particularly well is supported by the recent observations of von Gunten and colleagues.<sup>22</sup> They recorded mean aqueous humour ofloxacin concentrations of 530 (SD 350) ng ml<sup>-1</sup> following the administration of six 3 hourly single drop doses of 0.3% solution to cataract surgery patients.

Because these studies employed different antibiotic administration regimens, variable time periods between drug application and aqueous humour sampling and different assay procedures, direct comparison is difficult. However, although our observation that the mean aqueous humour ciprofloxacin concentration was 59% higher than that for norfloxacin was not statistically significant, this difference is consistent with previous data. The most important uncontrolled variable contributing to the broad range of aqueous humour antibiotic levels demon-

Table 1 Mean pre- and post-treatment bacterial counts (CFU/ml) isolated from lid swabs for patients receiving hourly drops of 0.3% norfloxacin and 0.3% ciprofloxacin for 6 hours. Data are presented for coagulase negative staphylococci and total bacteria

	Pretreatment (CFU/ml)	Post-treatment (CFU/ml)	<i>p</i> Value (paired <i>t</i> test)
Ciprofloxacin ( $n=18$ ):			
Coagulase negative staph	114.50	19.27	0.004
Total flora	230.94	38.05	0.019
Norfloxacin ( $n=20$ ):			
Coagulase negative staph	31.12	11.43	0.107
Total flora	55.84	23.38	0.133

strated in this study was probably the delay between drug administration and aqueous humour sampling.

Although this study showed variable aqueous humour concentrations of both antibiotics (as have previous studies), the mean concentrations were below the minimum inhibitory concentration (MIC) for clinical isolates of the organisms most likely to induce postsurgical endophthalmitis. Higher concentrations would probably be attained after ocular surgery or in the presence of inflammation, making topical quinolones useful in treatment of endophthalmitis. Ciprofloxacin would be a better option than norfloxacin for this purpose because of its superior spectrum of activity as well as the greater penetration observed. If the observation that ofloxacin has better penetration than both ciprofloxacin and norfloxacin<sup>21</sup> is confirmed, this agent may also prove useful despite the reduced sensitivity of some bacteria (notably *Pseudomonas aeruginosa*) to ofloxacin compared with ciprofloxacin.

This investigation has shown a statistically significant (sixfold) decrease in eyelid flora following six 1 hourly drops of ciprofloxacin. This agent may therefore be useful for presurgical prophylaxis, despite the likely inability of intraocular concentrations to inhibit bacteria postsurgically. Published data suggest that up to 82% of postoperative infections arise as a consequence of peroperative autologous inoculation of organisms adherent upon the ocular adnexae.<sup>23</sup> Furthermore, although the value of preoperative antibiotic prophylaxis remains unproved,<sup>9-24-28</sup> Speaker and Menikoff have shown that preoperative instillation of povidone iodine solution results in a reduction of postoperative infection rates.<sup>29</sup> Thus the prophylactic reduction of the preoperative ocular flora would appear to be desirable. Previous investigations have demonstrated appreciable differences in the abilities of topical antibiotics to decontaminate the external eye with chloramphenicol consistently proving less effective than aminoglycosides, particularly gentamicin.<sup>9-24</sup> As it is not possible to compare the efficacy of agents assessed in different studies because of methodological variations, it will be necessary to perform further trials to establish whether ciprofloxacin has the potential to decontaminate the external eye to an extent comparable with gentamicin and povidone iodine. If this proves to be the case the low toxicity of ciprofloxacin<sup>7-30</sup> and low incidence of resistance currently experienced will make it a useful alternative for the preoperative prophylaxis of ocular surgery.

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